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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03007780.4

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Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Cyclic benzimidazoles

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Cyclic benzimidazoles

Technical field

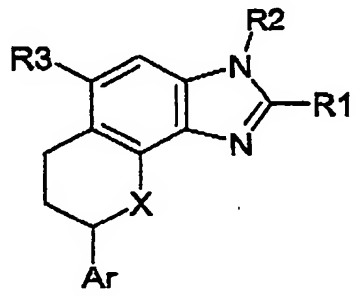
The invention relates to novel compounds, which are used in the pharmaceutical industry as active compounds for the production of medicaments.

Prior art

In European patent applications 266326 (which corresponds to US Patent 5,106,862), benzimidazole derivatives having a very broad variety of substituents are disclosed, which are said to be active as anti-ulcer agents.

Summary of the invention

The invention relates to compounds of the formula 1



(1)

in which

R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

X is O (oxygen) or NH and

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

wherein

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R6 is hydrogen, 1-4C-alkyl or halogen and

R7 is hydrogen, 1-4C-alkyl or halogen,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

Halogen within the meaning of the invention is bromo, chloro and fluoro.

1-4C-Alkyl represents a straight-chain or branched alkyl group having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl group.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl groups. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylmethyl and the cyclohexylethyl group.

1-4C-Alkoxy represents a group, which in addition to the oxygen atom contains one of the aforementioned 1-4C-alkyl groups. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy group.

1-4C-Alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. Examples which may be mentioned are the methoxymethyl, the methoxyethyl group and the butoxyethyl group.

1-4C-Alkoxycarbonyl (1-4C-alkoxy-CO-) represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy groups is bonded. Examples which may be mentioned are the methoxycarbonyl (CH_3O-C(O)-) and the ethoxycarbonyl group (CH_3CH_2O-C(O)-).

2-4C-Alkenyl represents a straight-chain or branched alkenyl group having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl and the 2-propenyl group (allyl group).

2-4C-Alkynyl represents a straight-chain or branched alkynyl group having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butynyl, 3-butynyl, and preferably the 2-propynyl, group (propargyl group).

Fluoro-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one or more fluorine atoms. An example which may be mentioned is the trifluoromethyl group.

Hydroxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by a hydroxy group. Examples which may be mentioned are the hydroxymethyl, the 2-hydroxyethyl and the 3-hydroxypropyl group.

Mono- or di-1-4C-alkylamino represents an amino group, which is substituted by one or by two - identical or different - groups from the aforementioned 1-4C-alkyl groups. Examples which may be mentioned are the dimethylamino, the diethylamino and the diisopropylamino group.

Mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl represents a 1-4C-alkylcarbonyl group, which is substituted by a mono- or di-1-4C-alkylamino groups. Examples, which may be mentioned, are the dimethylamino-methylcarbonyl and the dimethylamino-ethylcarbonyl group.

Fluoro-2-4C-alkyl represents a 2-4C-alkyl group, which is substituted by one or more fluorine atoms. An example which may be mentioned is the 2,2,2-trifluoroethyl group.

1-4C-Alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by a further 1-4C-alkoxy group. Examples which may be mentioned are the groups 2-(methoxy)ethoxy (CH_3-O-CH_2-CH_2-O-) and 2-(ethoxy)ethoxy (CH_3-CH_2-O-CH_2-CH_2-O-).

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkoxy-1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. An example which may be mentioned is the group 2-(methoxy)ethoxymethyl (CH_3-O-CH_2-CH_2-O-CH_2-).

Fluoro-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is completely or mainly substituted by fluorine, "mainly" meaning in this connection that more than half of the hydrogen atoms are replaced by fluorine atoms. Examples of completely or mainly fluoro-substituted 1-4C-alkoxy groups which may be mentioned are the 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy group

Fluoro-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by a fluoro-1-4C-alkoxy group. Examples of fluoro-1-4C-alkoxy-1-4C-alkyl groups are the 1,1,2,2-tetrafluoroethoxymethyl, the 2,2,2-trifluoroethoxymethyl, the trifluoromethoxyethyl and the difluoromethoxyethyl group.

1-7C-Alkyl represents a straight-chain or branched alkyl group having 1 to 7 carbon atoms. Examples which may be mentioned are the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl group.

Groups Ar which may be mentioned are, for example, the following substituents: 4-acetoxyphenyl, 4-acetamidophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 3-benzyloxy-4-methoxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3,5-bis(trifluoromethyl)phenyl, 4-butoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-chloro-6-fluorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-5-nitrophenyl, 4-chloro-3-nitrophenyl, 3-(4-chlorophenoxy)phenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 2,4-dihydroxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxy-5-hydroxyphenyl, 2,5-dimethylphenyl, 3-ethoxy-4-hydroxyphenyl, 2-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-hydroxy-5-nitrophenyl, 3-methoxy-2-nitrophenyl, 3-nitrophenyl, 2,3,5-trichlorophenyl, 2,4,6-trihydroxyphenyl, 2,3,4-trimethoxyphenyl, 2-hydroxy-1-naphthyl, 2-methoxy-1-naphthyl, 4-methoxy-1-naphthyl, 1-methyl-2-pyrrolyl, 2-pyrrolyl, 3-methyl-2-pyrrolyl, 3,4-dimethyl-2-pyrrolyl, 4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolyl, 5-ethoxycarbonyl-2,4-dimethyl-3-pyrrolyl, 3,4-dibromo-5-methyl-2-pyrrolyl, 2,5-dimethyl-1-phenyl-3-pyrrolyl, 5-carboxy-3-ethyl-4-methyl-2-pyrrolyl, 3,5-dimethyl-2-pyrrolyl, 2,5-dimethyl-1-(4-trifluoromethylphenyl)-3-pyrrolyl, 1-(2,6-dichloro-4-trifluoromethylphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(2-fluorophenyl)-2-pyrrolyl, 1-(4-trifluoromethoxyphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(4-ethoxycarbonyl)-2,5-dimethyl-3-pyrrolyl, 5-chloro-1,3-dimethyl-4-pyrazolyl, 5-chloro-1-methyl-3-trifluoromethyl-4-pyrazolyl, 1-(4-chlorobenzyl)-5-pyrazolyl, 1,3-dimethyl-5-(4-chlorphenoxy)-4-pyrazolyl, 1-methyl-3-trifluomethyl-5-(3-trifluoromethylphenoxy)-4-pyrazolyl, 4-methoxycarbonyl-1-(2,6-dichloro-

phenyl)-5-pyrazolyl, 5-allyloxy-1-methyl-3-trifluoromethyl-4-pyrazolyl, 5-chloro-1-phenyl-3-trifluoromethyl-4-pyrazolyl, 3,5-dimethyl-1-phenyl-4-imidazolyl, 4-bromo-1-methyl-5-imidazolyl, 2-butylimidazolyl, 1-phenyl-1,2,3-triazol-4-yl, 3-indolyl, 4-indolyl, 7-indolyl, 5-methoxy-3-indolyl, 5-benzyloxy-3-indolyl, 1-benzyl-3-indolyl, 2-(4-chlorophenyl)-3-indolyl, 7-benzyloxy-3-indolyl, 6-benzyloxy-3-indolyl, 2-methyl-5-nitro-3-indolyl, 4,5,6,7-tetrafluoro-3-indolyl, 1-(3,5-difluorobenzyl)-3-indolyl, 1-methyl-2-(4-trifluorophenoxy)-3-indolyl, 1-methyl-2-benzimidazolyl, 5-nitro-2-furyl, 5-hydroxymethyl-2-furyl, 2-furyl, 3-furyl, 5-(2-nitro-4-trifluoromethylphenyl)-2-furyl, 4-ethoxycarbonyl-5-methyl-2-furyl, 5-(2-trifluoromethoxyphenyl)-2-furyl, 5-(4-methoxy-2-nitrophenyl)-2-furyl, 4-bromo-2-furyl, 5-dimethylamino-2-furyl, 5-bromo-2-furyl, 5-sulfo-2-furyl, 2-benzofuryl, 2-thienyl, 3-thienyl, 3-methyl-2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-nitro-2-thienyl, 5-methyl-2-thienyl, 5-(4-methoxyphenyl)-2-thienyl, 4-methyl-2-thienyl, 3-phenoxy-2-thienyl, 5-carboxy-2-thienyl, 2,5-dichloro-3-thienyl, 3-methoxy-2-thienyl, 2-benzothienyl, 3-methyl-2-benzothienyl, 2-bromo-5-chloro-3-benzothienyl, 2-thiazolyl, 2-amino-4-chloro-5-thiazolyl, 2,4-dichloro-5-thiazolyl, 2-diethylamino-5-thiazolyl, 3-methyl-4-nitro-5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-methyl-2-pyridyl, 3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl, 2,6-dichloro-4-pyridyl, 3-chloro-5-trifluoromethyl-2-pyridyl, 4,6-dimethyl-2-pyridyl, 4-(4-chlorophenyl)-3-pyridyl, 2-chloro-5-methoxycarbonyl-6-methyl-4-phenyl-3-pyridyl, 2-chloro-3-pyridyl, 6-(3-trifluoromethylphenoxy)-3-pyridyl, 2-(4-chlorophenoxy)-3-pyridyl, 2,4-dimethoxy-5-pyrimidinyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 2-chloro-3-quinolinyl, 2-chloro-6-methoxy-3-quinolinyl, 8-hydroxy-2-quinolinyl and 4-isoquinolinyl.

2-4C-Alkenyloxy represents a group, which in addition to the oxygen atom contains one of the above-mentioned 2-4C-alkenyl groups. Examples, which may be mentioned, are the 2-butenyloxy, 3-butenyloxy, 1-propenyloxy and the 2-propenyloxy group (allyloxy group).

1-4C-Alkylcarbonyl represents a group, which in addition to the carbonyl group contains one of the abovementioned 1-4C-alkyl groups. An example which may be mentioned is the acetyl group.

Carboxy-1-4C-alkyl represents a 1-4C-alkyl group which is substituted by a carboxyl group. Examples, which may be mentioned, are the carboxymethyl and the 2-carboxyethyl group.

1-4C-Alkoxycarbonyl-1-4C-alkyl represents a 1-4C-alkyl group, which is substituted by one of the abovementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the Methoxycarbonylmethyl and the ethoxycarbonylmethyl group.

Aryl-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the abovementioned aryl groups. An exemplary preferred aryl-1-4C-alkyl group is the benzyl group.

Aryl-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the abovementioned aryl groups. An exemplary preferred aryl-1-4C-alkoxy group is the benzyloxy group.

1-4C-Alkylcarbonylamino represents an amino group to which a 1-4C-alkylcarbonyl group is bonded. Examples which may be mentioned are the propionylamino ($C_3H_7C(O)NH$-) and the acetylamino group (acetamido group) ($CH_3C(O)NH$-) .

1-4C-Alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the ethoxycarbonylamino and the methoxycarbonylamino group.

1-4C-Alkoxy-1-4C-alkoxycarbonyl represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy-1-4C-alkoxy groups is bonded. Examples which may be mentioned are the 2-(methoxy)-ethoxycarbonyl (CH_3-O-CH_2CH_2-O-CO-) and the 2-(ethoxy)ethoxycarbonyl group (CH_3CH_2-O-CH_2CH_2-O-CO-).

1-4C-Alkoxy-1-4C-alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxy-1-4C-alkoxycarbonyl groups. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonylamino and the 2-(ethoxy)ethoxycarbonylamino group.

Possible salts of compounds of the formula 1 - depending on substitution - are especially all acid addition salts. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are used in salt preparation - depending on whether a mono- or polybasic acid is concerned and on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can initially be obtained, for example, as process products in the production of the compounds according to the invention on the industrial scale, are converted into the pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to invention and their salts, if, for example, they are isolated in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1.

The compounds of the formula 1 have a chirality center in the 8-position. The invention thus relates to both enantiomers in any desired mixing ratio to another, including the pure enantiomers, which are a preferred subject of the invention.

Compounds to be mentioned particularly are those of formula 1,
in which

R1 is hydrogen or 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

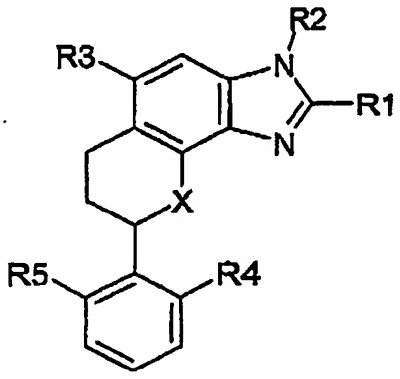
R3 is halogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen or 1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

X is O (oxygen) or NH and

Ar is a phenyl group, substituted by R4, R5, R6 and R7,
wherein
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,
R6 is hydrogen, 1-4C-alkyl or halogen and
R7 is hydrogen, 1-4C-alkyl or halogen,

and the salts of these compounds.

Among the compounds of formula 1, those of the formula 1a are preferred



(1a)

in which

R1 is hydrogen or 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen or 1-7C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, trifluoromethyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R5 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy and

X is O (oxygen) or NH,

and the salts of these compounds.

Among the compounds of formula 1, those of the formula 1a are particularly preferred in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-4C-alkyl, hydroxy-2-4C-alkyl or 1-4C-alkoxy-2-4C-alkyl and
R32 is hydrogen,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, group,

R4 is hydrogen,

R5 is hydrogen and

X is O (oxygen) or NH,

and the salts of these compounds.

Exemplary particularly preferred compounds are those of the formula 1a, in which R1, R2, R3, R4, R5 and X have the meanings given in the following table 1 (Me = CH_3):

Table 1

R1	R2	R3	R4	R5	X
Me	Me	CH_2OH	H	H	O
Me	Me	CH_2OCH_3	H	H	O
Me	Me	CONHMe	H	H	O
Me	Me	CON-pyrrolidine	H	H	O
Me	Me	$CONH(CH_2)_2OH$	H	H	O
Me	Me	$CONH(CH_2)_2OMe$	H	H	O
Me	Me	$CONH_2$	H	H	O
Me	Me	CH_2OH	H	H	NH
Me	Me	CH_2OCH_3	H	H	NH
Me	Me	CONHMe	H	H	NH
Me	Me	CON-pyrrolidine	H	H	NH
Me	Me	$CONH(CH_2)_2OH$	H	H	NH
Me	Me	$CONH(CH_2)_2OMe$	H	H	NH
Me	Me	$CONH_2$	H	H	NH

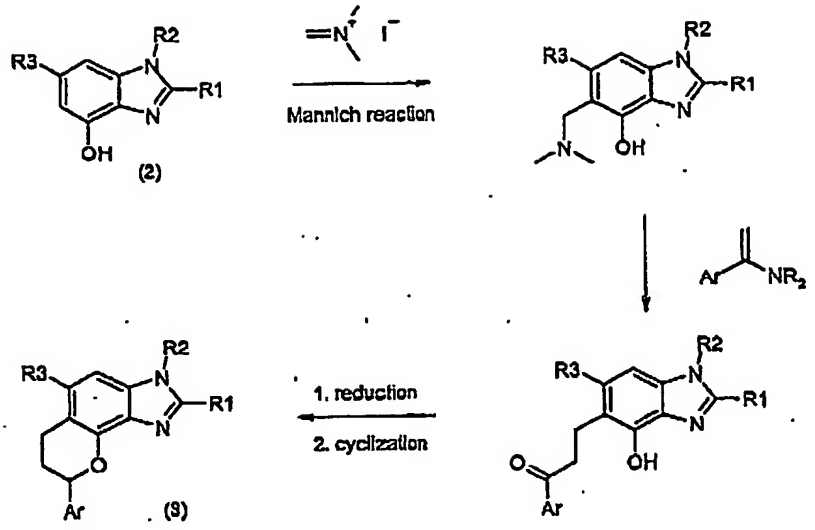
Particularly preferred are the compounds given as final products of formula 1 in the examples, and the salts of these compounds.

The compounds according to the invention can be synthesised from corresponding starting compounds, for example according to the reaction schemes given below (scheme 1 and scheme 2). The synthesis is carried out in a manner known to the expert, for example as described in more detail in the examples which follow the schemes.

The starting compounds are known, for example, from Gillespie et al., *J. Org. Chem.* **1960**, *25*, 942 (6-chloro-2-methyl-4-nitro-1(3)*H*-benzimidazole, J. R. E. Hoover, A. R. Day, *J. Amer. Chem. Soc.* **1955**, *77*, 4324 (4-nitro-1(3)*H*-benzimidazole-6-carboxamide) or A. R. Katritzky et al., *Heterocycles* **1995**, *41*, 345-352 (4-hydroxy-1-methyl-1*H*-benzimidazole) or they can be prepared using analogous process steps.

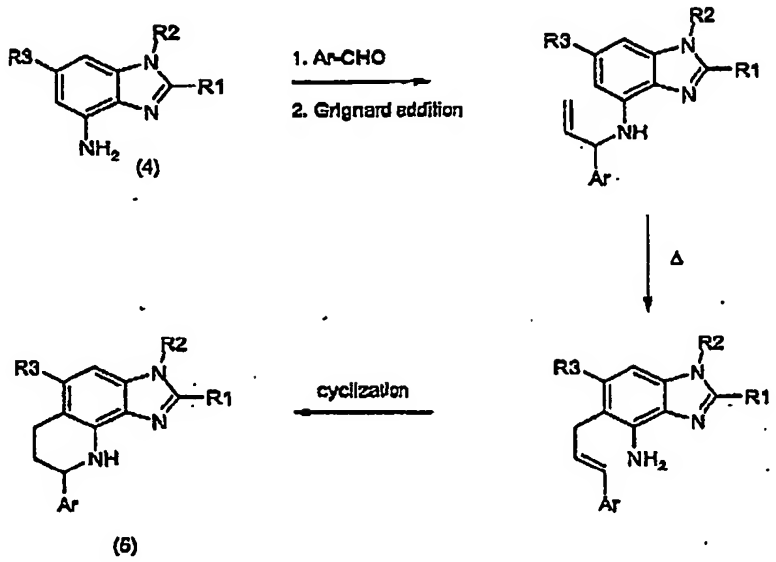
Scheme 1:

Preparation of compounds of the formula 1 where X = O (3), with any desired substituent R1, R2, R3 and Ar


R3
R2
N
R1
N
OH
(2)
=N+ I-
Mannich reaction
R3
R2
N
R1
N
N
OH
Ar
NR2
R3
R2
N
R1
N
O
Ar
(3)
1. reduction
2. cyclization
R3
R2
N
R1
N
OH
O
Ar

Scheme 2:

Preparation of compounds of the formula 1 where X = NH (5), with any desired substituent R1, R2, R3 and Ar



The preparation of the compounds of formula 1 where X = O [scheme 1, compounds (3)] can be carried out in a manner known to the person skilled in the art, for example, analogously as described in more detail in International Patent Applications WO 95/27714 and WO 03/014123.

Compounds of the formula 1 where X = NH [scheme 2, compounds (5)] can be obtained according to scheme 2, starting from corresponding substituted 4-amino-benzimidazoles known from literature.

The derivatization, if any, of the compounds obtained according to the above Schemes 1 and 2 (e.g. conversion of a group R3 into another group R3, or of R2 = H into another group e. g. R2 = 1-4C-alkyl) is likewise carried out in a manner known to the expert. If compounds where R3 = -CO-1-4C-alkoxy or R3 = -CO-NR31R32 are desired, an appropriate derivatization can be performed in a manner known to the expert (e. g. metal catalysed carbonylation of the corresponding halo compound or conversion of an ester into an amide) at the stage of the benzimidazoles of formula 2 or 4 (schemes 1 and 2) or more conveniently at a later point in time.

The following examples serve to illustrate the invention in greater detail without restricting it. Likewise, further compounds of the formula 1 or 2 whose preparation is not described explicitly can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques. The abbreviation min stands for minute(s), h for hour(s).

Examples

Final products of formula (1)

1. 2,3-Dimethyl-8-phenyl-3,6,7,8-tetrahydro-chromeno[7,8-a]imidazole- 5-carboxylic Acid Dimethylamide

10 ml Phosphoric acid (85 %) were heated to 80 °C for 10 min and then 850 mg (2.3 mmol) 7-hydroxy-6-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-3H-benzoimidazole-5-carboxylic acid dimethylamide were added during 10 min.. After heating at 80° C for 1 h, the reaction mixture was poured onto ice-water (20 ml) and neutralized with 2M sodium hydroxide solution. The filtrate was filtered off and crystallized from ethyl acetate to give 555 mg (68%) of the title compound as a white solid of m. p. 236°-237° C.

2. 5-Bromo-2,3-dimethyl-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-h]quinoline

A suspension of 2.0 g (5.6 mmol) 6-bromo-1,2-dimethyl-5-(3-phenyl-allyl)-1H-benzoimidazol-4-ylamine in 10 ml phosphoric acid (85 %) was heated to 130 °C for 20 min. The solution was poured onto crushed ice and the pH adjusted to pH = 9 by the addition of 6N sodium hydroxide solution. The mixture was extracted with dichloromethane/methanol (10:1), the organic phase separated, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by column chromatography on silica gel (toluene/dioxane/methanol = 6:3.8:0.2). Crystallization from diisopropyl ether yielded 1.7 g (84 %) of the title compound as a colourless solid. m.p. 206-210 °C.

3. 2,3-Dimethyl-8-phenyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-*h*]quinoline-5-carboxylic Acid Dimethylamide

To a solution of 1.5 g (4.2 mmol) 5-bromo-2,3-dimethyl-8-phenyl-6,7,8,9-tetrahydro-3H-imidazo[4,5-h]quinoline in 60 ml dimethylamine (5M solution in tetrahydrofuran) were added 95 mg (0.42 mmol) palladium(II) acetate and 0.66 g (2.5 mmol) triphenylphosphine. The mixture was transferred to an autoclave and carbonylated (6 bar carbon monoxide pressure, 120 °C) for 18 h. The reaction mixture was cooled down, poured into a mixture of saturated ammonium chloride solution (200 ml) and water (100 ml). The mixture was extracted with dichloromethane, the organic layer washed with water, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by column chromatography on silica gel (toluene/dioxane/methanol = 6:3.5:0.5). Crystallization from ethyl acetate yielded 0.43 g (29 %) of the title compound as a colourless solid. m.p. 167-170 °C.

Starting compounds and intermediates

A. 2-Benzyloxy-4-bromo-6-nitro-phenylamine

To a suspension of 50 g (325 mmol) 2-amino-3-nitrophenol, 45 g (325 mmol) potassium carbonate and 2 g (13 mmol) sodium iodide in 400 ml ethanol were added 47 ml (408 mmol) benzyl chloride and the mixture was heated to 80 °C. After 2 h, the reaction mixture was cooled down and the solvent was evaporated. The residue was dissolved in ethyl acetate and extracted with water. The organic layer was dried over anhydrous magnesium sulphate and evaporated. Coevaporation with dichloromethane (three times) led to a dark brown oily residue, which was dissolved in 400 ml acetonitrile. After addition of 63.4 g (356 mmol) N-bromosuccinimide, the reaction mixture was refluxed for 1 h. After cooling down, 400 g silica gel were added and the mixture was evaporated to dryness. The resulting solid was put on a column and the product was eluted with ethyl acetate/light petroleum ether (4:1). Evaporation of the eluent afforded a solid which was recrystallized from ethyl acetate/n-heptane to give 62 g (59 %) of the title compound as a red solid of m.p. 90 °C.

B. N-Acetyl-N-(2-benzyloxy-4-bromo-6-nitro-phenyl)-acetamide

A suspension of 20 g (62 mmol) 2-benzyloxy-4-bromo-6-nitro-phenylamine in 120 ml acetic anhydride and 2 ml methanesulphonic acid was heated to 120 °C. After complete reaction (15 min), excess acetic anhydride was evaporated in vacuo. The residue was dissolved in dichloromethane/water and neutralized with 6N aqueous sodium hydroxide. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Crystallization of the residue from ethyl acetate/n-heptane yielded 23.2 g (92 %) of the title compound as a cream-coloured solid of m.p. 148 °C.

C. N-(2-Amino-6-benzyloxy-4-bromo-phenyl)-acetamide

A suspension of 23 g (56 mmol) N-acetyl-N-(2-benzyloxy-4-bromo-6-nitro-phenyl)-acetamide, 5.5 g (34 mmol) iron(III) chloride and 13.8 g activated charcoal in 600 ml methanol was heated to reflux. To the reaction mixture were added 28 ml hydrazine hydrate (95 %) to maintain gentle reflux. After complete reaction (2 h), the reaction mixture was cooled down and filtered through celite. The filter cake was washed thoroughly with dichloromethane/methanol and the filtrate was evaporated to dryness. The residue was partitioned between dichloromethane/methanol and water. The organic layer was washed with brine, dried over anhydrous magnesium sulphate and evaporated. The residue was recrystallized from boiling ethyl acetate/n-heptane to give 12.3 g (65 %) of the title compound as a colourless solid of m.p. 185 °C.

D. N-(2-Benzyloxy-4-bromo-6-dimethylamino-phenyl)-acetamide

A suspension of 5 g (15 mmol) N-(2-amino-6-benzyloxy-4-bromo-phenyl)-acetamide in 80 ml methanol and 34 ml formaldehyde (37 %) was acidified with saturated methanolic hydrogen chloride to give a clear yellow solution. To the solution were added 1.5 g (24 mmol) sodium cyanoborohydride in small portions. After complete reaction (15 min), the mixture was neutralized with aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulphate and evaporated. Crystallization of the residue from ethyl acetate/n-heptane yielded 4.3 g (79 %) of the title compound as a colourless solid of m.p. 177 °C.

E. 4-Benzyloxy-6-bromo-1,2-dimethyl-1*H*-benzoimidazole

A suspension of 26.2 g (72 mmol) N-(2-benzyloxy-4-bromo-6-dimethylamino-phenyl)-acetamide in 180 ml phosphoryl chloride was heated to 70 °C for 24 h. After the reaction was completed, excess phosphoryl chloride was evaporated in vacuo. The residue was suspended in dichloromethane and carefully neutralized with 6N aqueous potassium hydroxide and water. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. Crystallization of the residue from ethyl acetate yielded 15.1 g (63 %) of the title compound as a colourless solid of m.p. 177-179 °C.

F. 7-Benzyloxy-2,3-dimethyl-3*H*-benzoimidazole-5-carboxylic Acid Dimethylamide

To a solution of 3 g (9.1 mmol) 4-benzyloxy-6-bromo-1,2-dimethyl-1*H*-benzoimidazole in 100 ml dimethylamine (3.2M solution in tetrahydrofuran) were added 0.3 g (1.3 mmol) palladium(II) acetate and 1.4 g (5.3 mmol) triphenylphosphine. The mixture was transferred to an autoclave and carbonylated (6 bar carbon monoxide pressure, 120 °C) for 16 h. The reaction mixture was cooled down, evaporated and the residue was dissolved in dichloromethane. The organic layer was extracted with water, dried over anhydrous magnesium sulphate and evaporated. Purification of the residue by column chromatography on silica gel using ethyl acetate yielded 2.3 g (78 %) of the title compound as a colourless solid of m.p. 159-160 °C.

G. 7-Hydroxy-2,3-dimethyl-3*H*-benzoimidazole-5-carboxylic Acid Dimethylamide

A solution of 2.3 g (7.1 mmol) 7-Benzyloxy-2,3-dimethyl-3*H*-benzoimidazole-5-carboxylic acid dimethylamide in 80 ml methanol was hydrogenated over 0.3 g 10% Pd/C (1 bar H_2) for 16 h. The catalyst was filtered off and the filtrate evaporated. The residue was crystallized from acetone to give 1.2 g (71 %) of the title compound as a colourless solid of m.p. 248 °C.

H. 6-Dimethylaminomethyl-7-hydroxy-2,3-dimethyl-3*H*-benzoimidazole-5-carboxylic Acid Dimethylamide

To a suspension of 2.0 g (8.6 mmol) 7-Hydroxy-2,3-dimethyl-*3H*-benzoimidazole-5-carboxylic acid dimethylamide in dichloromethane (80 ml) was added dropwise a suspension of 1.7 g (9.4 mmol) Eschenmoser's salts in dichloromethane (50 ml). After stirring for 3h at room temperature, the reaction mixture was poured into saturated sodium bicarbonate solution (100 ml) and extracted with dichloromethane (2 x 50 ml). The organic layers were dried over magnesium sulphate and concentrated in vacuo to give 2.0 g (82%) of the title compound as an orange foam. The compound was used for the next step without further purification.

^{1}H-NMR (200 MHz; DMSO): δ = 2.31 (s, 3H, Me), 2.58 (2s, 6H, 2 NC$\underline{H}_3$), 2.78 (s, 3H, NC$\underline{H}_3$), 3.02 (s, 3H, NC$\underline{H}_3$), 3.62 (m, 5H, C$\underline{H}_2$N, NC$\underline{H}_3$), 7.79 (s, 1H, Ar-$\underline{H}$).

I. 7-Hydroxy-2,3-dimethyl-6-(3-oxo-3-phenyl-propyl)-3H-benzoimidazole-5-carboxylic Acid Dimethylamide

2.0 g (6.9 mmol) 6-dimethylaminomethyl-7-hydroxy-2,3-dimethyl-*3H*-benzoimidazole-5-carboxylic acid dimethylamide and 1.8 g (10.3 mmol) 1-(1-phenyl-vinyl)-pyrrolidine were suspended in toluene (40 ml) and the reaction was refluxed over night. After cooling to room temperature, the solvent was concentrated in vacuo. The residue was purified by column chromatography on silica gel (dichloromethane / methanol = 14:1). Crystallization from ethyl acetate afforded 1.1 g (42%) of the title compound as a beige solid of m. p. 223°-224° C.

J. 7-Hydroxy-6-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-3H-benzoimidazole-5-carboxylic Acid Dimethylamide

To a suspension of 1.0 g (2.7 mmol) 7-hydroxy-2,3-dimethyl-6-(3-oxo-3-phenyl-propyl)-*3H*-benzoimidazole-5-carboxylic acid dimethylamide in ethanol (10 ml) were cautiously added 124 mg (3.3 mmol) sodium borohydride (60 % w/w dispersion in mineral oil) (exothermic reaction !) and the reaction was stirred for 2 h at room temperature. The reaction mixture was poured into saturated ammonium chloride solution (20 ml) and diluted with water (80 ml). The precipitate was filtered off and dried in vacuo to afford 880 mg (89%) of the title compound as a beige solid of m. p. 257°-260° C

K. 6-Bromo-2-methyl-4-nitro-1(3)*H*-benzoimidazole

To a suspension of 65 g (0.28 mol) 4-bromo-6-nitro-1,2-phenylenediamine in 600 ml ethanol were added 140 ml 5N hydrochloric acid. The reaction mixture was refluxed and 58 ml (0.56 mol) of 2,4-pentanedione were added in one portion. After 1 h, the mixture was cooled down, poured into 500 ml water and neutralized with conc. ammonia. The precipitate was collected, washed thoroughly with water and dried over phosphorus pentoxide to give 70.8 g (99 %) of the title compound of m.p. 229-231 °C.

L. 6-Bromo-1,2-dimethyl-4-nitro-1*H*-benzoimidazole

To a suspension of 4.3 g (107 mmol) sodium hydride (60 % *w/w* dispersion in mineral oil) in 25 ml N,N-dimethylformamide was slowly added a solution of 25 g (98 mmol) 6-bromo-2-methyl-4-nitro-1(3)*H*-benzoimidazole in 100 ml N,N-dimethylformamide at 0 °C. After 30 min at 0 °C, 15.2 g (107 mmol) methyliodide were added over 20 min. When the reaction was finished (45 min), 200 ml water were carefully added and the mixture was stirred for 1 h at room temperature. The precipitate was collected, washed thoroughly with water and dried over phosphorus pentoxide in vacuo. Recrystallization from methanol yielded 19.6 g (74 %) of the title compound as a colourless solid of m.p. 193-195 °C.

M. 6-Bromo-1,2-dimethyl-1*H*-benzoimidazol-4-ylamine

To a solution of 19 g (70 mmol) 6-bromo-1,2-dimethyl-4-nitro-1*H*-benzoimidazole in 250 ml methanol were added 13.7 g (84 mmol) iron(III) chloride and 6 g activated charcoal. The reaction mixture was heated to 80 °C and 17 ml hydrazine hydrate (95 %) were slowly added. After refluxing for 3 h, the hot reaction mixture was filtered through celite and the precipitate was washed with methanol and dichloromethane. The filtrate was evaporated to give a suspension, which was treated with n-heptane. The precipitate was collected, washed with n-heptane and dried in vacuo to give 13.3 g (79 %) of the title compound as a solid of m.p. 206-209 °C.

N. (6-Bromo-1,2-dimethyl-1*H*-benzoimidazol-4-yl)-(1-phenyl-allyl)-amine

6.4 g (26.7 mmol) 6-bromo-1,2-dimethyl-1*H*-benzoimidazol-4-ylamine, 8.5 g (80 mmol) benzaldehyde and 0.3 g p-toluenesulphonic acid monohydrate in 80 ml toluene were refluxed on a Dean-Stark-trap. After complete reaction, the mixture was evaporated to one third of its volume and diluted with 50 ml tetrahydrofuran. The mixture was cooled to 0 °C and 80 ml (80 mmol) vinylmagnesiumbromide (1M solution in tetrahydrofuran) were added during 45 min. After 30 min., the reaction mixture was hydrolyzed with saturated ammonium chloride solution, diluted with water and extracted with ethyl acetate. The organic phase was separated, washed with water, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 7:3). Crystallization from diisopropyl ether afforded 4.2 g (44 %) of the title compound as a colourless solid of m.p. 137-139 °C.

O. 6-Bromo-1,2-dimethyl-5-(3-phenyl-allyl)-1*H*-benzoimidazol-4-ylamine

A suspension of 3.8 g (10.7 mmol) (6-bromo-1,2-dimethyl-1*H*-benzoimidazol-4-yl)-(1-phenyl-allyl)-amine and 3.5 g p-toluenesulphonic acid monohydrate in 80 ml toluene was refluxed for 26 h. The suspension was poured into a mixture of 50 ml saturated sodium hydrogencarbonate solution and 150 ml water and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by column chromatography on silica gel (tolu-

ene/dioxane/methanol = 6:3.8:0.2). Crystallization from diisopropyl ether gave 2.45 g (64 %) of the title compound as a colourless solid of m.p. 186-189 °C.

Commercial utility

The compounds of the formula 1 and their salts have valuable pharmacological properties which make them commercially utilizable. In particular, they exhibit marked inhibition of gastric acid secretion and an excellent gastric and intestinal protective action in warm-blooded animals, in particular humans. In this connection, the compounds according to the invention are distinguished by a high selectivity of action, an advantageous duration of action, a particularly good enteral activity, the absence of significant side effects and a large therapeutic range.

"Gastric and intestinal protection" in this connection is understood as meaning the prevention and treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, gastric ulcer, peptic ulcer, including peptic ulcer bleeding, duodenal ulcer, gastritis, hyperacidic or medicament-related functional dyspepsia), which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, medicaments (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs and COX-inhibitors), chemicals (e.g. ethanol), gastric acid or stress situations. "Gastric and intestinal protection" is understood to include, according to general knowledge, gastroesophageal reflux disease (GERD), the symptoms of which include, but are not limited to, heartburn and/or acid regurgitation.

In their excellent properties, the compounds according to the invention surprisingly prove to be clearly superior to the compounds known from the prior art in various models in which the antiulcerogenic and the antisecretory properties are determined. On account of these properties, the compounds of the formula 1 and their pharmacologically acceptable salts are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine.

A further subject of the invention are therefore the compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

The invention likewise includes the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the abovementioned diseases.

The invention furthermore includes the use of the compounds according to the invention for the treatment and/or prophylaxis of the abovementioned diseases.

A further subject of the invention are medicaments which comprise one or more compounds of the formula 1 and/or their pharmacologically acceptable salts.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the pharmacologically active compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries or excipients in the form of tablets, coated tablets, capsules, suppositories, patches (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and it being possible to obtain a pharmaceutical administration form exactly adapted to the active compound and/or to the desired onset and/or duration of action (e.g. a sustained-release form or an enteric form) by means of the appropriate selection of the auxiliaries and excipients.

The auxiliaries and excipients which are suitable for the desired pharmaceutical formulations are known to the person skilled in the art on the basis of his/her expert knowledge. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

In general, it has proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose of approximately 0.01 to approximately 20, preferably 0.05 to 5, in particular 0.1 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds), as a rule, lower doses can be used. The establishment of the optimal dose and manner of administration of the active compounds necessary in each case can easily be carried out by any person skilled in the art on the basis of his/her expert knowledge.

If the compounds according to the invention and/or their salts are to be used for the treatment of the abovementioned diseases, the pharmaceutical preparations can also contain one or more pharmacologically active constituents of other groups of medicaments, for example: tranquillizers (for example from the group of the benzodiazepines, for example diazepam), spasmolytics (for example, bietamiverine or camylofine), anticholinergics (for example, oxyphencyclimine or phencarbamide), local anesthetics, (for example, tetracaine or procaine), and, if appropriate, also enzymes, vitamins or amino acids.

To be emphasized in this connection is in particular the combination of the compounds according to the invention with pharmaceuticals which inhibit acid secretion, such as, for example, H_2 blockers (e.g. cimetidine, ranitidine), H^+/K^+ ATPase inhibitors (e.g. omeprazole, pantoprazole), or further with so-called peripheral anticholinergics (e.g. pirenzepine, telenzepine) and with gastrin antagonists with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or of decreasing the side effects, or further the combination with antibacterially active substances (such as,

for example, cephalosporins, tetracyclines, penicillins, macrolides, nitroimidazoles or alternatively bismuth salts) for the control of Helicobacter pylori. Suitable antibacterial co-components which may be mentioned are, for example, mezlocillin, ampicillin, amoxicillin, cefalothin, cefoxitin, cefotaxime, imipenem, gentamycin, amikacin, erythromycin, ciprofloxacin, metronidazole, clarithromycin, azithromycin and combinations thereof (for example clarithromycin + metronidazole).

In view of their excellent gastric and intestinal protection action, the compounds of formula 1 are suited for a free or fixed combination with those medicaments (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs), which are known to have a certain ulcerogenic potency. In addition, the compounds of formula 1 are suited for a free or fixed combination with motility-modifying drugs.

Pharmacology

The excellent gastric protective action and the gastric acid secretion-inhibiting action of the compounds according to the invention can be demonstrated in investigations on animal experimental models. The compounds according to the invention investigated in the model mentioned below have been provided with numbers which correspond to the numbers of these compounds in the examples.

Testing of the secretion-inhibiting action on the perfused rat stomach

In Table A which follows, the influence of the compounds according to the invention on the pentagastrin-stimulated acid secretion of the perfused rat stomach after intraduodenal administration in vivo is shown.

Table A

No.	Dose (µmol/kg) i.d.	Inhibition of acid secretion (%)
1	1	79
3	1	60

Methodology

The abdomen of anesthetized rats (CD rat, female, 200-250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tubes just projected into the gastric lumen. The catheter leading from the pylorus led outward into the right abdominal wall through a side opening.

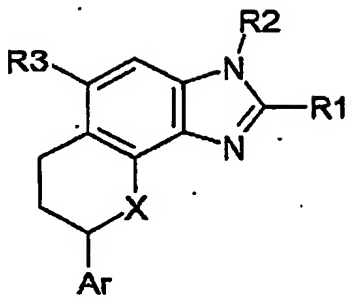
After thorough rinsing (about 50-100 ml), warm (37°C) physiological NaCl solution was continuously passed through the stomach (0.5 ml/min, pH 6.8-6.9; Braun-Unita I). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) and, by titration with a freshly prepared 0.01N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl were determined in the effluent in each case collected at an interval of 15 minutes.

The gastric secretion was stimulated by continuous infusion of 1 µg/kg (= 1.65 ml/h) of i.v. pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e. after determination of 2 preliminary fractions). The substances to be tested were administered intraduodenally in a 2.5 ml/kg liquid volume 60 min after the start of the continuous pentagastrin infusion.

The body temperature of the animals was kept at a constant 37.8-38°C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

Patent claims

1. Compounds of formula 1,



(1)

in which

R1 is hydrogen, halogen, hydroxyl, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl, hydroxy-1-4C-alkyl or mono- or di-1-4C-alkylamino,

R2 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl, hydroxy-1-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

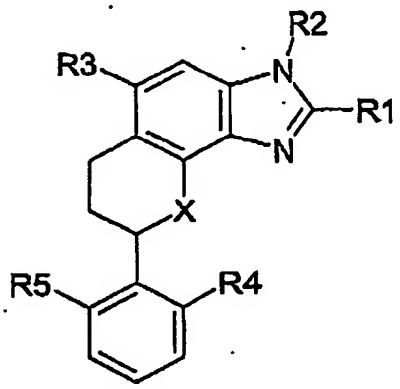
X is O (oxygen) or NH and

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,
wherein
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R6 is hydrogen, 1-4C-alkyl or halogen and
R7 is hydrogen, 1-4C-alkyl or halogen,
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,
and the salts of these compounds.

2. Compounds of formula 1 according to claim 1,
in which
R1 is hydrogen or 1-4C-alkyl,
R2 is hydrogen or 1-4C-alkyl,
R3 is halogen, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen or 1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,
X is O (oxygen) or NH and
Ar is a phenyl group, substituted by R4, R5, R6 and R7,
wherein
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,
R6 is hydrogen, 1-4C-alkyl or halogen and
R7 is hydrogen, 1-4C-alkyl or halogen,
and the salts of these compounds.

3. Compounds of formula 1 according to claim 1, characterized by the formula 1a,



(1a)

in which

R1 is hydrogen or 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen or 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, trifluoromethyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R5 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy and

X is O (oxygen) or NH,

and the salts of these compounds.

4. Compounds of formula 1 according to claim 1, characterized by the formula 1a in claim 3, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, 1-4C-alkyl, hydroxy-2-4C-alkyl or 1-4C-alkoxy-2-4C-alkyl and

R32 is hydrogen,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, group,

R4 is hydrogen,

R5 is hydrogen and

X is O (oxygen) or NH,

and the salts of these compounds.

5. A medicament comprising a compound as claimed in claim 1 and/or a pharmacologically acceptable salt thereof together with customary pharmaceutical auxiliaries and/or excipients.

6. The use of a compound as claimed in claim 1 and its pharmacologically acceptable salts for the prevention and treatment of gastrointestinal disorders.

Abstract

The invention relates to cyclic benzimidazoles of formula 1, in which the substituents and symbols have the meanings indicated in the description. The compounds have gastric secretion inhibiting and excellent gastric and intestinal protective action properties.